Photochemistry of 2-Alkylaminophenoxaz-3-ones.[1] I

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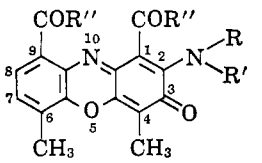
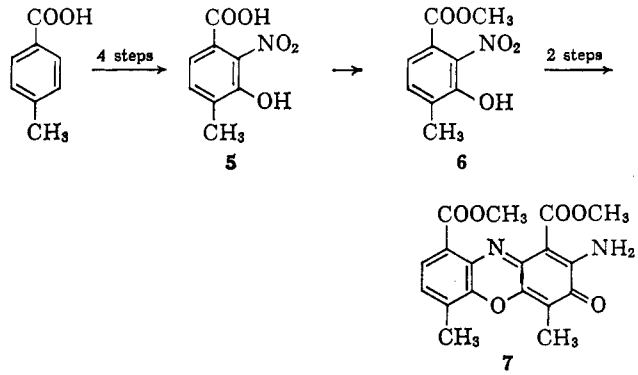
A number of 2-monoalkylaminophenoxaz-3-ones (**3**) have been synthesized and their photochemistry has been investigated. The methylamino- (**12**) and ethylaminophenoxaz-3-one (**13**) gave the oxazolophenoxazines **18** and **22**, respectively, on irradiation as well as thermolysis. The alkylaminophenoxaz-3-ones **14**, **15**, and **16**, incapable of forming oxazolophenoxazines, gave novel oxazolinophenoxazines **26**, **28**, and **29**, respectively, as the major products. The 2-aminophenoxaz-3-one **7** resulting from the photochemical dealkylation of the above three phenoxaz-3-ones was also isolated as a minor product. The results of the photochemical transformation have been rationalized by plausible mechanisms.

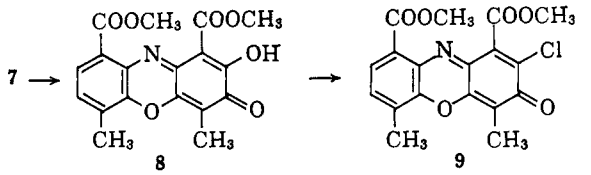
It has been reported[2] that N-methylactinomycin C_2 (**1**) undergoes photochemical demethylation leading to the formation of actinomycin C_2 (**2**). In an effort to delineate the mechanistic path and scope of this reaction, we have synthesized and irradiated a number of mono- and dialkylaminophenoxaz-3-ones, **3** and **4**, respectively. This paper reports the work on 2-monoalkylaminophenoxaz-3-ones.



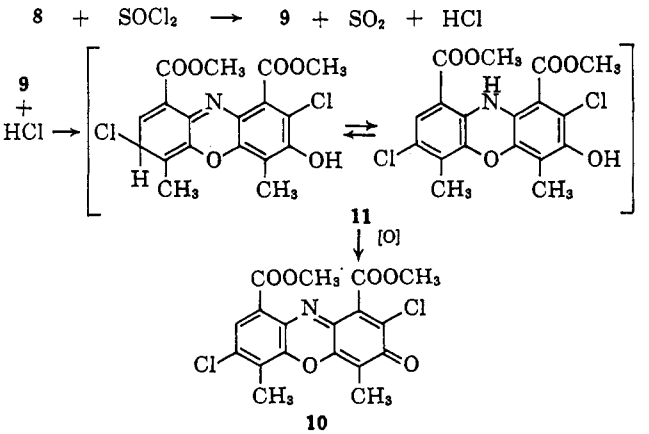
1, R = H; R′ = CH_3; R″ = peptide residue
2, R = H; R′ = H; R″ = peptide residue
3, R = H; R′ = alkyl; R″ = OCH_3
4, R = R′ = alkyl; R″ = OCH_3

Synthesis of 2-Alkylaminophenoxaz-3-ones.—On the premise that the peptide portion of the antibiotic plays no major role in this photochemical reaction, we chose to base our study on the simpler 4,6-dimethyl-1,9-dicarbomethoxy-2-alkylaminophenoxaz-3-ones (**3**). Fischer esterification of 2-nitro-3,4-cresotic acid (**5**),[3] obtained in four steps from *p*-toluic acid, gave the methyl ester **6**[4] which was converted in two steps to the 2-aminophenoxaz-3-one **7**.[5] The latter compound was heated under reflux with 50% aqueous acetic acid to give the corresponding 2-hydroxyphenoxaz-3-one **8**[5] in almost quantitative yield. Treatment with thionyl chloride in benzene containing pyridine then accomplished hydroxyl replacement, affording the 2-chlorophenoxaz-3-one **9**. This product represents a key intermediate in the present work since it can give rise to a series of mono- and dialkylaminophenoxaz-3-ones by treatment with appropriate amines.





The chloro compound **9** was also prepared using thionyl chloride in the absence of pyridine, but in this case it was accompanied by a by-product which appeared (elemental analysis) to be a dichlorophenoxazone. The latter product was also obtained from **9** by treatment with hydrogen chloride. The n.m.r. spectrum of the dichloro compound showed a single aromatic proton at τ 2.23 instead of the two doublets centered at τ 2.37 and 2.63 observed for **9**, thereby indicating chlorine substitution at either position 7 or 8 of the aromatic ring. The signals due to the carbomethoxy methyl groups in **9** and the dichloro compound are nearly identical. The aromatic ring methyl group of the dichloro product gives a singlet (τ 7.43) at slightly lower field than the corresponding methyl signal (τ 7.50) for the chlorophenoxaz-3-one **9**. This small downfield shift would suggest placement of the second chlorine atom *ortho* to the methyl group and structure **10** for the dichloro compound. A possible pathway for the formation of **10** from **9** is shown in the following scheme. It seems possible that, in the absence of pyridine, the hydrogen chloride formed during the reaction adds in a 1,10 manner to the conjugated system of **9** to give the dihydro-



(1) This work was supported by Contract No. DA-ARO(D)-31-124-G250 with the U. S. Army Research Office. Presented in part before the Organic Division at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1963.

(2) H. Brockmann, G. Pampus, and R. Mecke, *Ber.*, **92**, 3082 (1959).

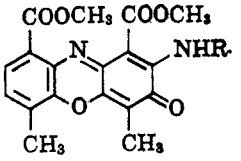
(3) B. Weinstein, O. P. Crews, M. A. Leaffer, B. R. Baker, and L. Goodman, *J. Org. Chem.*, **27**, 1389 (1962).

(4) S. J. Angyal, E. B. Bullock, W. E. Hanger, W. C. Howell, and A. W. Johnson, *J. Chem. Soc.*, 1592 (1957).

(5) H. Brockmann and H. Muxfeldt, *Chem. Ber.*, **91**, 1242 (1958).

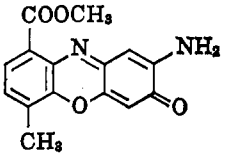
phenoxazone **11** which would be expected[2] to yield **10** on on air oxidation

The 2-alkylaminophenoxaz-3-ones **12–16** were prepared in excellent yields by treatment of the chlorophenoxazone **9** with the appropriate alkylamine in tetrahydrofuran as reported for the analogous preparation of N-methylactinomycin C_2 (**1**).[2] These compounds are light sensitive and care had to be taken to avoid prolonged exposure of their solutions to light. In general, the solubility of these compounds in common organic solvents increased with increase in size of the alkyl residue. The purity of all the phenoxaz-3-ones was ascertained by thin layer chromatography (t.l.c.) on silica gel G and development with 5% acetone in chloroform. No visualizing agent was necessary since all the phenoxaz-3-ones were colored.



12, R = CH_3
13, R = C_2H_5
14, R = $CH(CH_3)_2$
15, R = 
16, R = 
23, R = $COCH_3$

An examination of the n.m.r. spectra of compounds **12–16** in deuteriochloroform revealed that the nuclear and alkylamino side-chain protons appear at characteristic positions (*cf.* Experimental). Assignment of these peaks was in some cases aided by reference to an earlier spectral study of 6-methyl-9-carbomethoxy-2-aminophenoxaz-3-one (**17**).[6]



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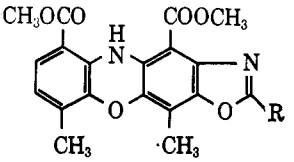
Photolysis of 2-Alkylaminophenoxaz-3-ones.—A solution of the 2-methylaminophenoxaz-3-one **12** in 25% methanol in benzene was irradiated for 2 hr. in an atmosphere of nitrogen using a Hanovia 654A lamp with a Pyrex filter cutting off at 350 mμ. Thin layer chromatographic assay of the product mixture indicated the presence of a highly fluorescent yellow compound along with unchanged starting material. A small amount of the pure fluorescent product could be obtained by liquid–liquid partition chromatography of the photolysis mixture on Celite using cyclohexane–dimethylformamide as the eluting system. The actual yield of the product determined fluorimetrically was 34%.

The same compound could also be obtained (58% yield) by the pyrolysis of **12** in bis(β-methoxyethyl) ether (diglyme, b.p. 162°).

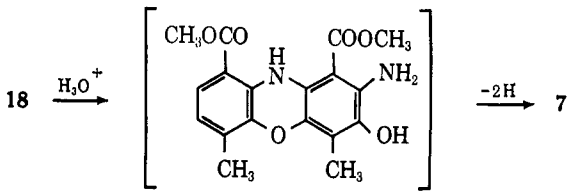
(6) C. Yembrick, Jr., Ph.D. Thesis, The Ohio State University, 1961, p. 54.

The elemental analysis and the strong fluorescence[7] of this product in solution are in good agreement with the oxazolophenoxazine structure **18**. This assign-



18, R = H
22, R = CH_3

ment is further supported by the n.m.r. spectrum which shows a singlet at τ 1.96 due to the oxazole proton.[8] Chemical evidence for the oxazolophenoxazine structure **18** was obtained by mild hydrolysis with dilute hydrochloride acid yielding the 2-aminophenoxaz-3-one **7** *via* autoxidation of the intermediate aminophenol **19**.



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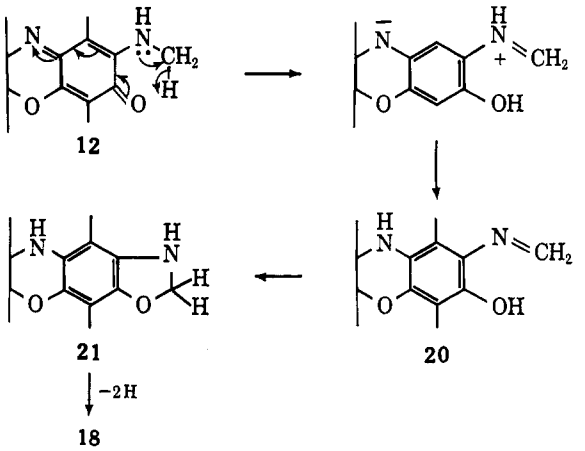
Having established the oxazole structure **18** for the irradiation and pyrolysis product, it is now pertinent to consider a possible pathway for this novel cyclization process.



The photochemically or thermally excited quinone carbonyl group of **12** may abstract a hydrogen from the methylamino side chain giving the Schiff base **20**. Cyclization to the oxazoline **21** followed by oxidation with unreacted starting material or air would provide the benzoxazole **18**.[9] The above mechanism is supported by the synthesis of **18** from **7**. A methanolic suspension of **7** was reduced catalytically to the aminophenol **19** and treated with formaldehyde to form the Schiff base **20** which gave **18** in good yield upon oxidation with air.

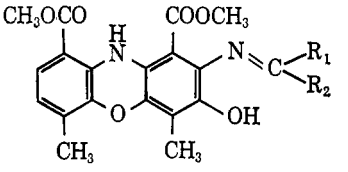
(7) A. M. Osman and I. Bassiouni, *J. Am. Chem. Soc.*, **82**, 1607 (1960).

(8) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 147 for benzoxazole.

(9) Alternatively, **18** may be formed by direct ring closure from **20** by a free-radical process. This mechanism has already been proposed by F. F. Stephen and J. D. Bower [*J. Chem. Soc.*, 1722 (1950)] for the formation of benzoxazoles from Schiff bases.

Irradiation or pyrolysis of 2-ethylaminophenoxaz-3-one **13** proceeded analogously, giving the methyloxazolophenoxazine **22**, which could also be synthesized from **7** by using acetaldehyde in place of formaldehyde. The n.m.r. spectrum of **22** showed the presence of the oxazole ring methyl at τ 7.42. Unlike **18**, the product **22** could not be hydrolyzed with dilute hydrochloric acid. However, hydrolysis under oxidative conditions with nitrous acid in dilute hydrochloric acid yielded the 2-acetamidophenoxaz-3-one **23** which was also prepared by the acetylation of **7**. The use of nitrous acid as an oxidant in the conversion of phenoxazines into phenoxaz-3-ones has been reported by Cavill and coworkers.[10]

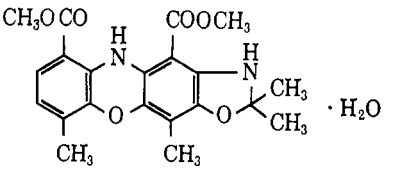
Irradiation of the 2-isopropylaminophenoxaz-3-one **14** was investigated since, in this case, ring closure to a benzoxazole is precluded. Thin layer chromatography of the total reaction mixture indicated that an unstable major product was formed which underwent color changes during the development of the chromatogram. It was also observed that the initial maxima at 231 and 450 mμ in the ultraviolet and visible spectrum of the total photolysis mixture slowly changed to maxima at 222, 244, 268, 310, and 376 mμ on standing. These observations suggest that the immediate product of the photolysis of **14** is the unstable Schiff base **24**. A chilled benzene solution of the photolysis product mixture deposited yellow crystals of a new stable product (30% yield) in addition to smaller amounts of the 2-aminophenoxaz-3-one **7**.



24, $R_1 = R_2 = CH_3$

The elemental analysis of the yellow product was in agreement with molecular formulas $C_{21}H_{24}N_2O_7$ or $C_{21}H_{22}N_2O_7$, allowing structural assignment as the hydrated oxazoline **25** or the hemiketal **26**. A decision in favor of the latter was based on the following considerations. (a) All attempts (*cf.* Experimental) to remove the molecule of water of crystallization were unsuccessful. (b) The ultraviolet spectrum of the product was not compatible with other phenoxazines prepared in our laboratory. (c) The infrared spectrum (Nujol mull) of the product exhibited bands at 1720 and 1665 cm.$^{-1}$ which could be assigned to the free and hydrogen-bonded ester carbonyl groups (*cf.* **26**). This observation is not in accord with structure **25** in which complete hydrogen bonding is to be expected. (d) Strong evidence in favor of structure **26** was also provided by n.m.r. data. The signals due to the aromatic protons and carbomethoxy and phenoxazine ring methyl groups appeared in the expected regions and could be accounted for by either of the two formulations. Two signals (3H each) at τ 8.40 and 8.47 must be assigned to the geminal C-methyl groups which are thus seen to be magnetically nonequivalent. This is to be expected only for structure **26**, which includes an asymmetric center. Two signals at τ 2.05 and 6.07 presumably due to the amino and hydroxyl protons (*cf.* **26**) were too weak to permit any definite assignments.

(10) G. W. K. Cavill, P. S. Clezy, and F. B. Whitfield, *Tetrahedron*, **12**, 139 (1961).



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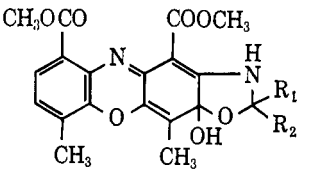
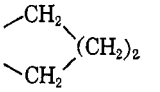
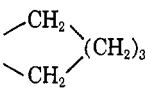


26, $R_1 = R_2 = CH_3$

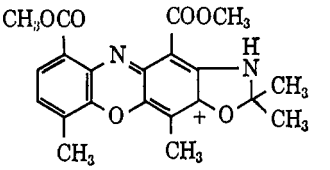


28, $R_1, R_2 =$



29, $R_1, R_2 =$

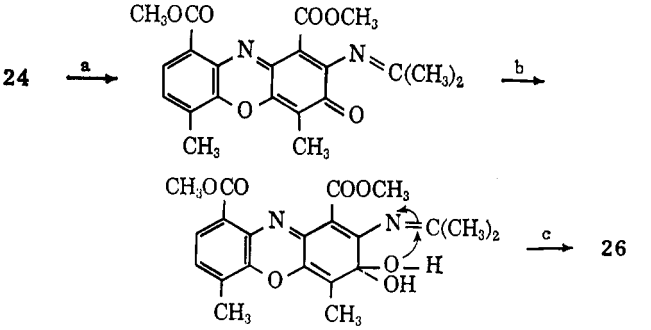
Acidic hydrolysis of **26** gave the expected aminophenoxaz-3-one **7**. The hemiketal **26** also underwent a noteworthy color reaction (not given by the alkylaminophenoxaz-3-ones, oxazoles, or the Schiff base **24**) with concentrated hydrochloric or sulfuric acid. The intense purple coloration can be accounted for by the formation of the resonance stabilized carbonium ion **27**.



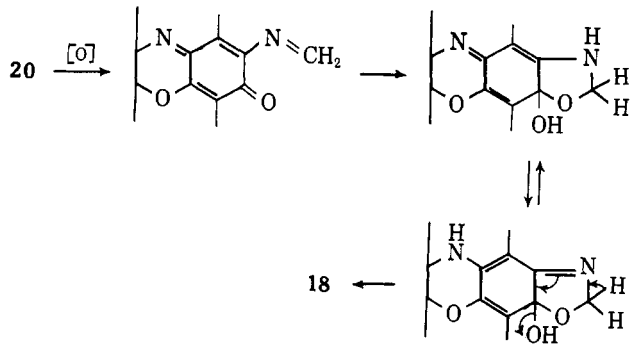
27

The hemiketal **26** was also prepared *via* the intermediate Schiff base **24** obtained from acetone and the reduced phenoxaz-3-one **19**.

By either route, we may consider the terminal heterocyclic ring to be formed by (a) oxidation to the corresponding phenoxaz-3-one, (b) hydration of the phenoxaz-3-one carbonyl group, and (c) intramolecular hydroxyl addition to the Schiff base.



It is possible that the benzoxazole products discussed earlier are likewise formed by way of hemiketal intermediates as illustrated below.



The oxazolines **28** and **29** were obtained by irradiation of the corresponding phenoxaz-3-ones **15** and **16** and their structures were in agreement with physical and chemical evidence. While a confirmatory synthesis of **29** was achieved using cyclohexanone and the reduced aminophenoxaz-3-one **19**, similar attempts to synthesize the lower homolog **28** gave only traces of the desired product.

We have been concerned with the relationship between our irradiation results and those of Brockmann and co-workers[2] who observed photochemical demethylation rather than the formation of the corresponding oxazolophenoxazine. In this connection, we plan to repeat our irradiation experiments employing phenoxazonediamides. This would provide a model closer to N-alkylactinomycin and might reveal a dependence of the over-all course of the photochemical reaction on the nature of the carboxy substituent.

Our results on the photochemistry of 2-cycloalkyliminophenoxaz-3-ones will be described in a future publication.

Experimental[11a,b]

Table I gives the melting points, yields, and literature references of intermediates leading to the synthesis of 4,6-dimethyl-1,9-dicarbomethoxy-2-hydroxyphenoxaz-3-one (**8**).

TABLE I

Compound	M.p., °C.	% yield	ref.
p-Toluic acid (Matheson Coleman and Bell)	179–181	..	..
3-Nitro-*p*-toluic acid	187–189	88	*a*
3-Acetamido-*p*-toluic acid	275–276	88	*a*
3-Acetamido-2-nitro-*p*-toluic acid	254–255	52	*a*
2-Nitro-3,4-cresotic acid (**5**)	185–186	57	*a*
Methyl 2-nitro-3,4-cresotate (**6**)	114–115	79	*b*
4,6-Dimethyl-1,9-dicarbomethoxy-2-aminophenoxaz-3-one (**7**)	197–198 (darkening)	65	*c*
4,6-Dimethyl-1,9-dicarbomethoxy-2-hydroxyphenoxaz-3-one (**8**)	270 (darkening)	90	*c*

[a] See ref. 3. [b] See ref. 4. [c] See ref. 5.

(11) (a) The melting points were determined on a Kofler microscope hot stage and are uncorrected. The analyses were carried out by Micro-Tech Laboratories, Skokie, Ill. The infrared spectra were determined on a Perkin-Elmer 221 spectrophotometer. The ultraviolet absorption spectra were measured by means of a Bausch and Lomb recording spectrophotometer Model 505. N.m.r. spectra were recorded on Varian H. R. 60 and A-60 instruments at 60 Mc. using deuteriochloroform as solvent and tetramethylsilane (0 c.p.s.) as an internal standard. (b) The purity of all 2-unsubstituted phenoxaz-3-ones, and oxazolo- and oxazolinophenoxazines was established by t.l.c. on silica gel G using 5% acetone in chloroform.

4,6-Dimethyl-1,9-dicarbomethoxy-2-chlorophenoxaz-3-one (**9**) **and 4,6-Dimethyl-1,9-dicarbomethoxy-2,7-dichlorophenoxaz-3-one** (**10**).—To a suspension of 0.150 g. of finely powdered **8** in 10 ml. of dry benzene was added 1 ml. of thionyl chloride and 0.5 ml. of pyridine and the reaction mixture was refluxed for 0.75 hr. The residue obtained by the removal of thionyl chloride and benzene under reduced pressure was treated with water and the product was extracted with chloroform. It was purified by passing its chloroform solution through a short column of alumina (activity IV) and crystallization from methyl ethyl ketone, yielding 112 mg. (70%) of **9** melting at 274°: λ_{max}^{MeOH} 224 mμ (ε 15,969), 262 (11,272), 358 (9394), 500 (4697); ν_{max}^{KBr} 2950, 1740, 1617, 1580, 1500 cm.$^{-1}$; n.m.r. 2.37, 2.63 (ring protons), 5.97, 6.04 (O-methyl), 7.50, 7.79 (ring methyl).

Anal. Calcd. for $C_{18}H_{14}ClNO_6$: C, 57.50; H, 4.02. Found: C, 57.49; H, 4.01.

If the above reaction was carried out in the absence of pyridine with a large excess of thionyl chloride, a dichloro compound (**10**, 10%) melting at 257–259° could be isolated by preparative t.l.c. on a silica gel G plate (25 × 38 × 0.8 cm.) using 5% acetone in chloroform. The desired band was eluted with 50% ethyl acetate in chloroform. The same product was also formed upon treating the benzene solution of **9** with hydrogen chloride and allowing the reaction mixture to stand at room temperature for several hours: λ_{max}^{MeOH} 230 mμ (ε 25,431), 264 (15,587), 370 (15,587), 480 (9844); ν_{max}^{KBr} 3080, 3050, 2955, 1740, 1630, 1590, 1560, 1500 cm.$^{-1}$; n.m.r. 2.23 (ring proton), 5.95, 6.03 (O-methyl), 7.43, 7.78 (ring methyl).

Anal. Calcd. for $C_{18}H_{13}Cl_2NO_6$: C, 52.70; H, 3.19; Cl, 17.28; N, 3.41. Found: C, 53.00; H, 3.39; Cl, 16.90; N, 3.78.

General Procedure for the Preparation of 4,6-Dimethyl-1,9-dicarbomethoxy-2-alkylaminophenoxaz-3-ones.—A solution of **9** in dry tetrahydrofuran (1.0 ml./mg.) was treated with a large excess (10–15-fold) of the appropriate alkylamine and allowed to stand in dark for 18–20 hr. in an icebox (room temperature if the amine had a boilong point above 30°). Excess amine and the solvent were removed under reduced pressure. A chloroform solution of the residue was shaken several times with water, dried, and evaporated. The product was crystallized from methyl ethyl ketone or ethyl acetate. The following 2-alkylaminophenoxaz-3-ones were prepared by this procedure.

4,6-Dimethyl-1,9-dicarbomethoxy-2-methylaminophenoxaz-3-one (**12**) was obtained in 98% yield: m.p. 177–179° (transformation to a yellow product); λ_{max}^{MeOH} 220 mμ (ε 46,295), 253 (49,072), 425 (40,739), 445 (43,512); ν_{max}^{KBr} 3334, 3305, 2950, 1722, 1620, 1590, 1522 cm.$^{-1}$; n.m.r. 2.40, 2.74 (ring protons), 3.61 (NH), 6.07, 6.08 (O-methyl), 6.97 (N-methyl), 7.50, 7.80 (ring methyl).

Anal. Calcd. for $C_{19}H_{18}N_2O_6$: C, 61.61; H, 4.90; N, 7.56. Found: C, 61.77; H, 5.05; N, 7.57.

4,6-Dimethyl-1,9-dicarbomethoxy-2-ethylaminophenoxaz-3-one (**13**) was obtained in 89% yield: m.p. 164–166° (transformation to a yellow product); λ_{max}^{MeOH} 224 mμ (ε 26,895), 252 (34,209), 425 (31,134), 446 (41,513); ν_{max}^{KBr} 3300, 2950, 1722, 1615, 1583, 1509 cm.$^{-1}$; n.m.r. 2.40, 2.75 (ring protons), 3.63 (NH), 6.00, 6.02 (O-methyl), 6.62 (methylene), 7.50, 7.80 (ring methyl), 8.68 (C-methyl).

Anal. Calcd. for $C_{20}H_{20}N_2O_6$: C, 62.44; H, 5.24; N, 7.29. Found: C, 62.25; H, 5.10; N, 7.12.

4,6-Dimethyl-1,9-dicarbomethoxy-2-isopropylaminophenoxaz-3-one (**14**) was obtained in 88% yield: m.p. 177–179°; λ_{max}^{MeOH} 226 mμ (ε 22,310), 254 (29,481), 424 (27,888), 444 (31,075); ν_{max}^{KBr} 3450, 3290, 2980, 2960, 1720, 1710, 1625, 1583, 1510 cm.$^{-1}$; n.m.r. 2.40, 2.74 (ring protons), 3.59 (NH), 6.00, 6.02 (O-methyl), 7.47, 7.78 (ring methyl), 8.68 (C-methyl).

Anal. Calcd. for $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.57; N, 7.03. Found: C, 63.40; H, 5.63; N, 7.22.

4,6-Dimethyl-1,9-dicarbomethoxy-2-cyclopentylaminophenoxaz-3-one (**15**) was obtained in 90% yield: m.p. 133–134°; λ_{max}^{MeOH} 228 mμ (ε 15,280), 252 (22,071), 428 (21,222), 446 (23,769); ν_{max}^{KBr} 3430, 3310, 2950, 2875, 1730, 1710, 1620, 1580, 1505 cm.$^{-1}$; n.m.r. 2.40, 2.75 (ring protons), 3.47 (NH), 6.01, 6.04 (O-methyl), 7.50, 7.80 (ring methyl), 8.28 (methylene).

Anal. Calcd. for $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 64.91; H, 5.68; N, 6.45.

4,6-Dimethyl-1,9-dicarbomethoxy-2-cyclohexylaminophenoxaz-3-one (**16**) was obtained in 87% yield: m.p. 161–162°, λ_{max}^{MeOH} 224 mμ (ε 20,168), 250 (25,430), 426 (22,599), 446 (26,307);

ν_{max}^{KBr} 3430, 2940, 2855, 1725, 1622, 1585, 1500 cm.$^{-1}$; n.m.r. 2.40, 2.74 (ring protons), 3.49 (NH), 6.00, 6.05 (O-methyl), 7.49, 7.80 (ring methyl), 8.60 (methylene).

Anal. Calcd. for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.69; H, 6.04; N, 6.58.

4,6-Dicarbomethoxy-9,11-dimethyl-5H-oxazolo[4,5-*b*]phenoxazine (18). A. By Photolysis.—A solution of 40 mg. of **12** in 225 ml. of benzene and 75 ml. of methanol was irradiated in an atmosphere of nitrogen for 2 hr. using a Hanovia 654A lamp equipped with a Pyrex filter cutting off at 350 mμ. T.l.c. of the reaction mixture indicated the presence of starting material and a greenish yellow fluorescent product with traces of polar material near the origin. The amount of fluorescent product in the photolysis mixture as determined by an Aminco-Bowman spectrofluorometer was found to be 33.70%.

Approximately 8 mg. of the photolysis mixture was subjected to liquid–liquid partition chromatography (l.l.p.c.) using cyclohexane–dimethylformamide as the solvent system. The stationary phase (8 ml.) was distributed homogeneously on 8 g. of 545 Celite (Johns-Mansville) using a mechanical shaker. The column (23 × 1.5 cm.) was slurry packed in the mobile phase, mixed thoroughly with approximately 1.5 g. of Celite, and packed into the column using mobile phase. The fluorescent product was eluted first, well separated from other materials. Removal of cyclohexane from these eluates left a residue which was then diluted with chloroform and washed several times with water. Evaporation of the dry chloroform extract gave 1.5–2 mg. of pure **18**.

B. By Pyrolysis.—A solution of 50 mg. of **12** in 15 ml. of bis(β-methoxyethyl) ether (diglyme, b.p. 162°) was refluxed for 1.5 hr. Excess solvent was removed under reduced pressure on a steam bath. A chloroform solution of the residue was passed through a short column of alumina (activity IV). The product (29 mg., 58%) crystallized as needles from ethyl acetate.

C. From 7.—A suspension of 25 mg. of **7** in 50 ml. of methanol was hydrogenated over platinum oxide (10 mg.) during 1 hr. The dihydro compound **19** was treated *in situ* with 8 ml. of 30–40% aqueous formaldehyde solution. The system was evacuated and the reaction mixture was stirred for 45 min. The catalyst was removed and the filtrate was concentrated to about 5 ml. under reduced pressure, diluted with water, and extracted with chloroform. The residue from the dry chloroform extract was crystallized from ethyl acetate to yield 17 mg. (66%) of **18**: m.p. 281–282°; λ_{max}^{MeOH} 226 mμ (ε 40,519), 252 (36,915), 419 (16,576); ν_{max}^{KBr} 3430, 2950, 1700, 1509 cm.$^{-1}$; n.m.r. −1.41 (NH), 1.96 (oxazole proton), 2.59, 3.46, (ring protons), 5.90, 6.08 (O-methyl), 7.70, 7.83 (ring methyl).

Anal. Calcd. for $C_{19}H_{16}N_2O_6$: C, 61.96; H, 4.38; N, 7.61. Found: C, 62.02; H, 4.66; N, 7.63.

4,6-Dicarbomethoxy-2,9,11-trimethyl-5H-oxazolo[4,5-*b*]phenoxazine (22). A. By Photolysis.—A solution of 40 mg. of **13** in 225 ml. of benzene and 75 ml. of methanol was photolyzed following the procedure for compound **12** and 1.5–2 mg. of pure **22** was obtained by l.l.p.c. of the photolyzed mixture. The yield of **22** as determined by a spectrofluorometer was found to be 52.50%.

B. By Pyrolysis.—The phenoxaz-3-one **13** was pyrolyzed following the procedure for compound **12**. Pure **22** was obtained in 64% yield after crystallization from aqueous methanol.

C. From 7.—The procedure for the preparation of **18** was slightly modified for the preparation of **22**.

A suspension of 100 mg. of crude **7** in 100 ml. of methanol was hydrogenated over platinum oxide (30 mg.) during 1.5 hr. The reaction mixture was cooled with ice and treated with 5 ml. of freshly distilled acetaldehyde in 5 ml. of methanol. The system was evacuated and the reaction mixture was stirred for 2 hr. during which time the temperature rose to 25°. The catalyst and the insoluble product were filtered and the product was dissolved by washing with hot methanol. Evaporation of the combined methanolic filtrates gave 90 mg. (86%) of pure **22**, m.p. 244–246°. An analytical sample was prepared by crystallization from aqueous methanol: m.p. 244–246°; λ_{max}^{MeOH} 226 mμ (ε 39,002), 250 (32,884), 416 (15,295); ν_{max}^{KBr} 3430, 2950, 1703, 1570, 1560, 1510 cm.$^{-1}$; n.m.r. −1.41 (NH), 2.70, 3.59 (ring protons), 5.89, 6.04 (O-methyl), 7.42 (oxazole ring methyl), 7.77, 7.92 (ring methyl).

Anal. Calcd. for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.67; H, 4.83; N, 7.41.

Hydrolysis of 18.—A solution of 30 mg. of **18** in 12 ml. of chloroform and 12 ml. of methanol was treated with 3 ml. of 2 *N* hydrochloric acid and stirred at room temperature for 46 hr. The reaction mixture was neutralized with saturated sodium bicarbonate solution and diluted with water, and the products were extracted with chloroform. The residue from the dry chloroform solution was chromatographed on a short column of alumina (activity IV) with chloroform to yield 17 mg. of **7** and 2.5 mg. of **8**, identified by t.l.c., melting point and infrared spectrum.

4,6-Dimethyl-1,9-dicarbomethoxy-2-acetamidophenoxaz-3-one. A. From 7.—To 50 mg. of crude **7** suspended in 30 ml. of cold benzene was added 0.2 ml. of pyridine and 2 ml. of acetyl chloride. The reaction mixture was stirred for 15 hr. during which time the temperature rose to 25°; it was then evaporated to dryness under reduced pressure and the chloroform solution of the residue was shaken successively with dilute hydrochloric acid, sodium bicarbonate solution, and water. It was dried and passed through a short column of alumina (activity IV). The crude product was crystallized from ethyl acetate to yield 25 mg. of pure **23**.

B. By Oxidative Hydrolysis of 22.—Attempts to hydrolyze **22** with dilute hydrochloric acid in refluxing methanol were unsuccessful; most of the starting material was recovered.

A solution of 20 mg. of **22** in 25 ml. of methanol was treated with 4 ml. of 2 *N* hydrochloric acid and 1 ml. of 10% sodium nitrite solution and allowed to stand at room temperature for 30 min. The reaction mixture was diluted with water and extracted with chloroform. The chloroform extract was washed successively with dilute sodium bicarbonate solution and water. Pure **23** (2 mg.), identical with the authentic sample, was obtained by preparative t.l.c. of the crude product: m.p. 258–261°; λ_{max}^{MeOH} 237 mμ (ε 27,088), 401 (20,714); ν_{max}^{KBr} 3435, 3295, 2950, 1730, 1600, 1595 cm.$^{-1}$; n.m.r. 2.39, 2.52 (ring protons), 5.95, 5.98 (O-methyl), 7.42 (acyl methyl), 7.69, 7.75 (ring methyl).

Anal. Calcd. for $C_{20}H_{18}N_2O_7$: C, 60.30; H, 4.55; N, 7.03. Found: C, 60.58; H, 4.63; N, 7.38.

4,6-Dicarbomethoxy-2,2,9,11-tetramethyl-11a-hydroxyoxazolino[4,5-*b*]phenoxazine (26). A. By Photolysis.—A solution of 40 mg. of **14** in 225 ml. of benzene and 75 ml. of methanol was irradiated for 2 hr. using a Hanovia 654A lamp equipped with a Pyrex filter cutting off at 300 mμ in an atmosphere of nitrogen. T.l.c. of the reaction mixture indicated the presence of some polar material which remained at the origin, traces of starting material, and the product, which moved with considerable streaking. The spot due to the product changed colors from dark orange to green and finally to light orange. The ultraviolet and visible spectrum of the crude reaction mixture in methanol initially exhibited maxima at 231 and 450 mμ but slowly changed to a spectrum having maxima at 222, 244, 268, 310, and 376 mμ when the methanolic solution stood at room temperature for several hours.

Solvent was removed under reduced pressure and the residue, in a minimum of benzene, was allowed to stand in an icebox for several hours. The yellow product (30%) which separated was filtered and washed several times with small amounts of benzene until t.l.c. showed a single spot. The gummy residue from the benzene filtrate upon trituration with methanol gave **7** (22%) identified by t.l.c., mixture melting point, and infrared spectrum.

B. From 7.—A suspension of 50 mg. of **7** in 100 ml. of methanol was hydrogenated over platinum oxide (30 mg.) during 1 hr. The dihydro compound **19** was treated *in situ* with a large excess (5 ml.) of acetone and stirred for 18–20 hr. in an atmosphere of hydrogen. The insoluble material was dissolved by adding chloroform and the catalyst was removed by filtration. The residue from the filtrate was dissolved in a minimum of benzene and allowed to stand in an icebox for several hours. The yellow product (51.7%) which separated was filtered and washed several times with small amounts of benzene until t.l.c. showed a single spot. The identity of the oxazolines obtained by procedures A and B was established by t.l.c., mixture melting point, and infrared spectrum. An analytical sample of **26** was prepared by crystallization from ether–petroleum ether (b.p. 30–60°): m.p. 183–185°; λ_{max}^{MeOH} 222 mμ (ε 16,656), 244 (25,818), 268 (17,489), 310 (11,659), 376 (24,985); ν_{max}^{Nujol} 3300, 3160, 1720, 1665, 1620, 1560 cm.$^{-1}$; n.m.r. 2.30, 3.05 (ring protons), 5.94, 6.14 (O-methyl), 7.60, 7.95 (ring methyl), 8.40, 8.47 (oxazoline ring methyl), 2.05 (amino proton), 6.70 (hydroxyl proton).

Anal. Calcd. for $C_{21}H_{22}N_2O_7$ (**26**): C, 60.86; H, 5.35. Calcd. for $C_{21}H_{22}O_6N_2 \cdot H_2O$ (**25**): C, 60.56; H, 5.81. Found: C, 60.60; H, 5.61.

In an attempt to remove the molecule of water, the analytical sample was crystallized thrice from benzene and dried 32 hr. a 100° and 0.5 hr. at 140° under vacuum over phosphorus pentoxide. A sublimation of the compound was also tried without success.

Anal. Found: C, 60.63, 60.82; H, 5.28, 5.56.

4,6-Dicarbomethoxy-2-spirocyclopentyl-9,11-dimethyl-11a-hydroxyoxazolino[4,5-*b*]phenoxazine (28). A. By Photolysis.—A solution of 40 mg. of **15** in 225 ml. of benzene and 75 ml. of methanol was photolyzed following the procedure for compound **12**. Solvent was removed under reduced pressure and the residue in a minimum of benzene, was allowed to stand in an icebox for several hours. The yellow product (12 mg.) which separated was washed several times with small amounts of benzene until t.l.c. showed a single spot. The gummy residue from the benzene filtrate was subjected to preparative t.l.c. on a 20 × 20 cm. silica gel G plate with 20% acetone in chloroform to yield approximately 4 mg. of **7**.

B. From 7.—The oxazoline **28** was formed in trace amounts only, as indicated by t.l.c. when its preparation was attempted from reduced **7** and cyclopentanone; most of the unreacted **7** was recovered from the reaction mixture.

An analytical sample of **28** was prepared by passing its chloroform solution through a short column of alumina (activity IV) and crystallization from ethyl acetate: m.p. 180° (darkening); λ_{max}^{MeOH} 222 mμ (ε 12,388), 244 (21,237), 270 (14,158), 312 (9733), 376 (20,352); ν_{max}^{KBr} 3430, 2950, 2875, 1715, 1675, 1622, 1560 cm.$^{-1}$; n.m.r. 2.30, 2.90 (ring protons), 5.92, 6.10 (O-methyl), 7.61, 7.93 (ring methyl), 8.04 (methylene). The compound was insufficiently soluble in deuteriochloroform; therefore, the signals due to the amino and hydroxyl protons were not observed.

Anal. Calcd. for $C_{23}H_{24}N_2O_7$: C, 62.72; H, 5.49. Found: C, 62.42; H, 5.60.

4,6-Dicarbomethoxy-2-spirocyclohexyl-9,11-dimethyl-11a-hydroxyoxazolino[4,5-*b*]phenoxazine (29). A. By Photolysis.—A solution of 40 mg. of **16** in 225 ml. of benzene and 75 ml. of methanol was photolyzed following the procedure for compound **12**, and the oxazoline **29** (36%) and 2-aminophenoxaz-3-one **7** (13.5%) were isolated from the photolysis mixture.

B. From 7.—The same compound **29** was prepared in 36.6% yield in the same manner as oxazoline **28** by using cyclohexanone instead of acetone. The analytical sample of **29** was prepared by crystallization from ethyl acetate: m.p. 189–192°; λ_{max}^{MeOH} 222 mμ (ε 15,520), 240 (24,649), 268 (17,346), 310 (11,868), 376 (23,736); ν_{max}^{KBr} 3430, 2940, 2860, 1720, 1705, 1675, 1620, 1560 cm.$^{-1}$; n.m.r. 2.32, 3.06 (ring protons), 5.95, 6.20 (O-methyl), 7.65, 7.98 (ring methyl), 8.30 (methylene). The compound was insufficiently soluble in deuteriochloroform; therefore, the signals due to the amino and hydroxyl protons were not observed.

Anal. Calcd. for $C_{24}H_{26}N_2O_7$: C, 63.42; H, 5.77; N, 6.14. Found: C, 63.29; H, 6.02; N, 6.25.

Hydrolysis of Oxazolines 26, 28, and 29.—A solution of 15 mg. of oxazoline **26** in 10 ml. of methanol was treated with 2 ml. of 2 *N* hydrochloric acid and heated for 10 hr. at 55°. On allowing the reaction mixture to stand overnight at room temperature, dark red crystals (3 mg.) of 2-hydroxyphenoxaz-2-one (**8**), identified by t.l.c., mixture melting point, and infrared spectrum, were obtained. The filtrate was neutralized with sodium bicarbonate solution and extracted with chloroform. The residue from the dried chloroform extract was chromatographed on a short column of alumina (activity IV) with chloroform to yield 3 mg. of pure 2-aminophenoxaz-3-one **7**.

The same compound **7** could be isolated from the acid hydrolysis of **28** and **29** under similar conditions.

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Resin Acids. IV. 12-Hydroxyabietic Acid and Its Reduction[1]

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12α-Hydroxyabietic acid has been obtained by reaction of levopimaric acid with hypochlorous acid in basic solution. The structure was proved by independent synthesis from levopimaric acid peroxide. Hydrogenation furnished two dihydro derivatives and one tetrahydro derivative whose structure and stereochemistry were established. The o.r.d. curves of 12-keto-8α-H-abietanes are discussed.

In an earlier paper[1] it was demonstrated that the structure of a hydroxyabietic acid obtained by selenium dioxide oxidation of abietic acid was not 12-hydroxyabietic acid as originally proposed[5] but 9α-hydroxyabietic acid (**1**). We now report the preparation of authentic 12α-hydroxyabietic acid (**2**), proof of its structure, and a study of its reduction.

When levopimaric acid (**3**) was dissolved in dilute base and treated with hypochlorous acid, there was formed in 35% yield a substance, $C_{20}H_{20}O_3$, m.p. 164–166°, $[\alpha]^{24}D$ −146°, which was obviously a hydroxy acid (formation of a methyl ester which exhibited hydroxyl absorption in the infrared) and differed from the isomeric substance prepared by selenium dioxide oxidation of abietic acid.[1,5]

The ultraviolet spectrum of the new hydroxy acid was essentially identical with the ultraviolet spectrum of abietic acid and exhibited maxima at 236, 242, and 250 mμ (ϵ_{max}^{242} 24,800). The n.m.r. spectrum,[6] in addition to resonances at 1.07, 1.10 (doublets, J = 7, of isopropyl side chain), 0.77 (C-10 methyl), and 1.24 p.p.m. (C-4 methyl), had two signals in the vinyl region which were very similar to analogous signals in the n.m.r. spectrum of abietic acid, one relatively complex resonance at 5.50 corresponding to H-7 and a second sharp singlet at 5.85 p.p.m. corresponding to H-14. In addition there was a broad one-proton peak at 4.28 p.p.m. characteristic of a proton geminal to a hydroxyl group.

The ultraviolet and n.m.r. spectra suggested that the new substance was either 6- or 12-hydroxyabietic acid.

(1) Previous paper: W. Herz and H. J. Wahlborg, *J. Org. Chem.*, **30**, 1881 (1965).

(2) Department of Chemistry, The Florida State University. Work at The Florida State University supported in part by a grant from the National Science Foundation (GP-1492).

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(4) Naval Stores Laboratory, Olustee, Fla. One of the laboratories of The Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(5) L. Fieser and W. P. Campbell, *J. Am. Chem. Soc.*, **60**, 159 (1938).

(6) N.m.r. spectra were run in deuteriochloroform, unless otherwise specified, on a Varian A-60 spectrometer purchased with the aid of a grant from the National Science Foundation to The Florida State University. Frequencies are given in parts per million with tetramethylsilane serving as internal standard. Multiplicities are expressed by conventional symbols.